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The Honorable Patricia Roberts Harris
Secretary
Department of Health, Education, and Welfare
Washington D.C. 20201

DNA

Dear Secretary Harris:

I am writing in regard to two changes in the NIH Recombinant DNA Guidelines published in the Federal Register on November 30th. I have followed closely developments in the recombinant DNA field during the past four years. I am engaged in an extensive study of the evolution of policy for recombinant DNA technology in the United States and Great Britain, and I also teach a course on the history of the recombinant DNA controversy at the University of Michigan. The following remarks address two aspects of the proposed actions: i) relations between the arguments advanced in the Federal Register and the proposed changes in controls; and ii) the policy implications of these changes.

I. The "E.coli K-12/P1 proposal (p.69218). (The arguments supporting this proposal are given in the NIH director's "decision document," p. 69234 f.)

According to this proposal, which applies to 80-85% of all work in the field, experiments would require registration only with committees within the institutions engaged in the work. There would be no external oversight and the present system, which requires registration with the NIH Office of Recombinant DNA Activities, would be dismantled. Thus this proposal entails the removal of most of the present controls for E.coli K-12 host-vector systems.

The justification for this major change in policy is given in section III-B of the "decision document," p.69236. This section purports to demonstrate a "low probability" for harmful effects from experiments conducted at the "P1" level of physical containment. The material is organized under a series of subheadings in question form, such as: "What is the Likelihood of E.coli K-12 Escape from a P1 Laboratory?" I assume that these questions are rhetorical in thrust and that certain answers to them are implied. For convenience, I have numbered these subheadings "1"-"12." Detailed comments on this section are attached. To summarize my conclusions:

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NOTE: OS sent original to OGC for direct reply

1. A fundamental but unexamined assumption of the analysis in section III-B (see discussion following question 1) is that all work with E.coli host-vector systems would be conducted at the "P1" level of physical containment in which various safeguards would be maintained. Specifically the analysis assumes a ban on mouth pipetting and a requirement that all wastes be decontaminated before disposal--two major means of preventing exposure to or dissemination into the environment of large numbers of microorganisms containing recombinant DNA.*

It needs emphasis that there is currently no requirement (only a recommendation) that institutions require workers in this field to be trained in good laboratory practice. Experience in the environmental and occupational health and safety fields shows that safety standards can be difficult to maintain even when the dangers are well understood and mandatory controls and training programs are in place. Is it then not wildly optimistic to assume that all workers in this expanding and competitive field will maintain high standards of laboratory practice in the absence of controls and of required training? Under such conditions, a more plausible assumption is that P1 containment will not be maintained, that accidents will occur, and that there will be cases of exposure to large numbers of E.coli bacteria.

2. Many of the arguments developed in section III-B** have been used previously to justify the revision of the guidelines (resulting in substantial lowering of containment levels and weakening of administrative controls) published in December, 1978. (See, e.g., the arguments following questions 2,3,4,6,7,10 (in part), and 12.) All of the remaining arguments, except one, are based on data that is either controversial (e.g. the results of the Rowe-Martin experiment, used in response to question 10); or incomplete (e.g. the results of the experiments of Levy et al. on survival of E.coli host-vector systems in the mammalian intestinal tract, used in response to question 10); or inconclusive (e.g. the data collected by Richmond, used in response to question 8, and the results of Brown and Burnett, used in response to question 9); or not sufficiently comprehensive to justify an across-the-board removal of controls (e.g. the results of Chan et al. used in response to question 5). In the remaining case (question 11), the argument is not based on empirical data but on the opinions of scientists who either do or do not believe that strains of E.coli producing modified peptide hormones might induce autoimmune responses in humans. These conflicting opinions are hardly conclusive. In fact, they underscore the need for empirical assessment, as proposed in the NIH risk assessment plan of September, 1979.

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* Mouth pipetting and disposal of active biological wastes are not the only routes of exposure or dissemination. Other routes, e.g. injection, which can occur either through cuts with broken glassware or through accidents with hypodermic syringes, are not explored in this document.

** See attached analysis.

3. The NIH justification makes use of a scheme for assessing recombinant DNA risks developed by Dr. Sydney Brenner of the Laboratory of Molecular Biology in Cambridge, England.* The scheme is being used by the British authorities to assess recombinant DNA projects. The description of the Brenner scheme (p.69237) suggests to the uninformed that this approach to risk assessment and the values embedded in it are in harmony with the arguments and values used to justify the "E.coli K-12/P1" proposal. In fact, there are important differences between the two approaches which lead to very different conclusions regarding both containment precautions and general policy. Specifically:

i)The Brenner scheme is being used within a regulatory system which covers all recombinant DNA activities in the public and the private sectors. Work is screened by a broadly constituted committee (the Genetic Manipulation Advisory Group) appointed by the Secretary for Education and Science. The committee advises the Health and Safety Commission, which is responsible for promulgating and implementing regulations. Important elements of the British system are:

a) Central registry and screening of recombinant DNA activities.

b) Central collection of health data for individuals working in recombinant DNA facilities.

c) Strong representation of the interests of employees at every level of the policy-making process.

Elements b) and c) have no counterparts in the current system of controls in this country and element a) would be eliminated if the "E.coli K-12/P1" proposal is accepted.

ii) According to the Brenner scheme, recombinant DNA hazards are assessed on a scale of 0 (no harmful outcome) to 1 (harmful outcome probable). Work assessed at the lowest end of the scale is carried out under category I (comparable to P1) conditions. Work assessed at the highest end of the scale is carried out under category IV (comparable to P4) conditions. The hazard of a particular process is determined according to the estimated values of three factors--f, the estimated fraction of DNA sequences capable of producing an outcome, h, the probability of expression, and a, the probability of access of a gene product, or the sequence itself, to an appropriate target--and the estimated probability of a harmful outcome which they jointly imply. It should be noted that:

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* This paper is in section 11 of the "Background Documents on E.coli K-12/P1 Recommendation," available from the NIH Office of Recombinant DNA Activities.

a) In the use of the Brenner scheme, the burden of proof falls on the investigator to show that an experiment poses minimal hazard. In contrast, in the "EK1/P1" proposal, a very broad range of experiments with E.coli is assumed to be of minimal hazard.

b) The Brenner assessment considers only risks to exposed individuals, not those to populations. This is a conservative approach because bacteria capable of affecting individuals may not be sufficiently virulent or produced in sufficiently large numbers to survive and spread from person to person.

These differences are reflected in the substantive outcomes of the "EK1/P1" proposal and of application of the Brenner scheme. To give just one example, the cloning of the gene for a human hormone is classified as a Category IV or III experiment in Britain, if an EK1 host-vector system is used* Under the "EK1/P1" proposal, containment would be P1.

In summary, the arguments developed in section III-B of the decision document do not support the contention that the probability of a harmful outcome of work with E.coli K-12 host-vector systems is always very low. Much of the evidence cited was used to justify revision of the guidelines in 1978. The new evidence that has come to light since that time does not justify the sweeping changes contemplated in this proposal. In addition, no empirical data are available on the hazards of organisms that are engineered to produce proteins (an area of great industrial importance). Neither the immediate physiological effects or autoimmune effects of such bacteria in human and animal hosts have been studied.

Given the weakness of the arguments supporting the "EK1/P1" proposal and the uncertainties and lack of empirical data still associated with the risks, particularly of industrially important processes, the most prudent course would be to continue to use the present NIH guidelines and to modify them on a case-by-case basis as the relevant risk assessment experiments are carried out and consensus regarding their implications is reached. The "EK1/P1" proposal calls for particular caution because it represents a major reversal of the policy of prevention and anticipation of hazard that originally informed the move to develop guidelines for the recombinant DNA field. If this change in policy is accepted, a most important means for monitoring developments in the recombinant DNA field will be lost. At the same time, NIH will lose its moral influence on the policies adopted in other countries. Certainly, a precipitous rush to dismantle controls which coincides far more obviously with mounting industrial momentum in this field than with any breakthrough in understanding of its potential impact is bound to be regarded with skepticism.

*See pp.12-13 of Annex B of the Brenner report, section 11 of the "Background Documents."

II. System of Voluntary Registration, Certification, and Compliance (p.69229). (Arguments supporting this proposal are given in the NIH director's "decision document," p.69247 f.)

The proposal entails the development by NIH of a voluntary system of compliance to cover recombinant DNA research, development, and applications in the private sector. This proposal should be rejected for the following reasons:

1. There is much evidence from other areas of technological development which shows that systems of voluntary compliance are not generally effective. Deviant behavior is a fairly common phenomenon of our time, and certainly it is not unknown in the field of occupational health and safety.* It would be naive to suppose that such behavior will not occur under a system of voluntary compliance for the recombinant DNA field, especially in view of the intense competitive pressures acting in this field.

2. In implementing a system of voluntary compliance, NIH would assume quasi-regulatory functions with respect to the private sector. Yet the NIH director has repeatedly stated that he has no wish for the Institutes to take on the responsibility of assuring compliance with its standards. As Dr. Fredrickson stated in December, 1977:

> I do want to ....reiterate something that I have, personally, speaking for NIH, now said in testifying before at least four congressional committees on this question of legislative proposals to regulate recombinant DNA experiments, and that is roughly the following. It is that I believe it a conflict of interest for the National Institutes of Health to be both the sponsor, the conductor, and the regulator in the sense of the enforcer, of guidelines for this type of research.
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> We feel it an important responsibility on our part to engage to the maximum our own resources and those of the broad community which we support in the preparation and promulgation of standards, but we cannot conduct here on this campus roughly ten percent of the research which is now under NIH aegis and pretend also to police the entire country, or to be the regulator in the sense that agencies long or recently established for the purpose of regulation could do. We have not the expertise. We have not the desire. **

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* See, e.g. the testimony of Dr.J. Finklea, Hearings of the Subcommittee on Health and Environment, Committee on Interstate and Foreign Commerce, U.S. House of Representatives, 95th Congress, p.287f.

** Transcript of the proceedings of the December 15-16, 1977 meeting of the Advisory Committee to the Director, NIH, in Department of Health, Education, and Welfare, Recombinant DNA Research (U.S.Government Printing Office: Washington D.C., September, 1978), vol.III, p.459.

If the NIH has neither the expertise nor the desire to assure compliance with its guidelines, it is clearly a mistake for it to initiate a system of control for the private sector, voluntary or otherwise.

Some now confidently assert that controls are unnecessary because the potential hazards of this field are minuscule (a view which contrasts with those widely held a few years ago). It is well to bear in mind how often similar statements with regard to the hazards of other fields of science and technology have proved to be mistaken, and at what cost to those affected. Until the implications of the recombinant DNA field are clear, a prudent course would be to develop uniform mandatory controls in order to provide a public record of recombinant DNA activities and to assure compliance with federal standards.

The need for controls to cover recombinant DNA activities in the private sector has been recognized for some time.*This has always been a major problem with the scope of the NIH guidelines. As you know, Senator Adlai Stevenson is proposing to introduce legislation to meet this need. I hope that his efforts will receive your strong support.

Sincerely,

Susan Wright
Lecturer in the History
of Science

2 enclosures

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*Senator Edward Kennedy and Senator Jacob Javits to President Gerald Ford, July 19, 1976. (Repr. in DHEW, Recombinant DNA Research (March, 1978), II, pp.158-60.)

Oversight Report of the Subcommittee on Science, Technology, and Space, Committee on Commerce, Science, and Transportation, U.S. Senate, August 1978, p.vii.

National Institutes of Health,"Environmental Impact Assessment of a Proposal to Release Revised NIH Guidelines for Research Involving Recombinant DNA Molecules," Federal Register 43 (28 July 1978),33098. This document states that "pending legislation introduced in 1978 provides the most promising solution yet available for establishing national standards for the use of recombinant DNA techniques." The **legislation referred to, H.R.11192, was not passed.**